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<p>(21) International Application Number: PCT/BG98/00011</p> <p>(22) International Filing Date: 18 June 1998 (18.06.98)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>101 856</td> <td>26 August 1997 (26.08.97)</td> <td>BG</td> </tr> <tr> <td>102 375</td> <td>7 April 1998 (07.04.98)</td> <td>BG</td> </tr> </table> <p>(71) Applicant (for all designated States except US): PEGAS LTD. [BG/BG]; Shipka Street 28, 1504 Sofia (BG).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): TOPALOV, Iovtcho Boyanov [BG/BG]; Shipka Street 28, 1504 Sofia (BG). NEDKOVA, Margarita Stoyanova [BG/BG]; Kompl.Borovo, B1.229, Ap.19, 1680 Sofia (BG).</p> <p>(74) Agent: SLABOVA, Roumiana Stefanova; Irin Patent Ltd., Leonardo Da Vinci Street 3, 1124 Sofia (BG).</p>		101 856	26 August 1997 (26.08.97)	BG	102 375	7 April 1998 (07.04.98)	BG	<p>(81) Designated States: AL, AM, AU, BA, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KE, KP, KR, LR, LS, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TM, TR, UA, US, UZ, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
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102 375	7 April 1998 (07.04.98)	BG						
<p>(54) Title: INJECTABLE, BIOCOMPATIBLE, HYDROPHILIC GEL, PROCESS FOR ITS PREPARATION AND APPLICATION</p> <p>(57) Abstract</p> <p>The invention relates to an injectable, biocompatible, hydrophilic gel for replenishment of missing areas of man's and mammals' soft tissue or for increasing the turgor of the said tissue. The gel is based on polyacrylamide and contains further a well-tolerated by the patient antibiotic and/or antiseptic, the said gel particle size being between 0.005 and 2 mm. The invention relates also to a process for preparation and application of the gel.</p>								

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INJECTABLE, BIOCOMPATIBLE, HYDROPHILIC GEL, PROCESS FOR ITS PREPARATION AND APPLICATION

Technical field

5 The invention relates to an injectable, biocompatible, hydrophilic gel for replenishment of missing areas of the soft tissue of man or mammals, or for increasing the soft tissue turgor in various cosmetic operations. The invention relates also to a process for preparation and application of the gel.

10 State of the art

It is known from Enzymology, Dimitar Kolev, Nauka i Izkustvo Publishing House, Sofia 1988, page 316, and from US patent No. 4 743 258 dated 10.05.1988, that the different tissues and systems in the human organism are indifferent to the polyacrylamide gel. The said gel is used for temporary
15 immobilization of enzymes in the form of gel microspheres, so that after their introduction in the blood system of the organism (Enzymology, Dimitar Kolev), the enzymes remain in an active state but are hidden for the protection system receptors of the organism. The substrates and products of the enzymes thus immobilized are more low-molecular and can pass by
20 diffusion through the pores of the polyacrylamide spheres.

It is known also from Application for invention No. 100 240/21.12.1995 published in the Official Bulletin of the Patent Office, issue 3/1997, that the polyacrylamide gel is used for replenishment of cavities resulting from suppurative processes, road accidents, burns or necessitated surgical
25 interventions. The gel is obtained on the basis of polyacrylamide and includes an anesthetic.

A disadvantage of the known methods for introduction of the gel in the tissues is that in a certain number of cases there occurs infection followed by suppuration and rejection of the gel. Gels obtained according to the
30 known methods are difficult to manipulate due to their great viscosity.

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What is more, the application of the known gels, which are offered in concentrations up to 3 per cent, leads in the course of time to loss of part of the injected gel mass (approximately 20 per cent). As a result, additional
5 reshaping of tissues is often necessitated. Another disadvantage of the known gels applied in cosmetic corrections of tissues is that they cannot be used for replacement or obtaining of harder body tissues like, for example, retracted muscles of amputation stumps or imitating the shape of an erected penis. This is due to the fact that polyacrylamide gels used are
10 prepared in a consistence allowing their taking (although difficult) in a syringe. The said gels are relatively soft and are more suitable for shaping of soft tissues like breasts, lips and other face or belly areas. Harder gels obtained through increased polyacrylamide concentration, over 3.1 per cent for example, are even more viscous and their taking in the syringe
15 constitutes a serious problem.

The task of the invention is to create an injectable, biocompatible hydrophilic gel allowing to eliminate the danger of infection.

A further task of the invention is to create a gel allowing preservation of the reshaped tissue volume for a practically indefinite period of time.

20 It is also a task of the invention to create a gel, injectable at polyacrylamide concentration over 3 per cent, and at the same time to improve and facilitate the technique of the gel's introduction in the patient's tissues.

Technical essence of the invention

The gel according to the invention is a spatially cross-linked structure of
25 polyacrylamide incorporating an aqueous solution of NaCl and an anaesthetic. The authors of the present invention have ascertained that the addition of an antibiotic and/or antiseptic in suitable concentrations between 0.1 and 0.5 per cent (w/v) sharply reduces the rejection of the gel by the patient. The authors have ascertained also that the ground gel with
30 particles size between 0.005 and 2 mm allows for the use of a gel with

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higher polyacrylamide concentration and that such a gel can be applied in replacement of harder tissues in the body - corrections unknown to have been made so far. What is more, the authors have ascertained an
5 unexpected effect from the application of the gel according to the present invention at polyacrylamide concentrations between 3 and 4 per cent, the said concentrations allowing preservation of the reshaped tissue volume for a practically indefinite period of time.

Gel particle size is preferably between 0.2 and 0.8 mm.

10 The antibiotic used according to the invention may be selected from a large group of broad-spectrum antibiotics and practically depends solely on the patient's tolerability towards the selected antibiotic. Rocephine, Gentamycin, Cephalexin, Amikacin and other antibiotics can be included in the gel composition. 5-Nitrox, Nelidix, Flagyl, etc. can be selected as
15 antiseptics. The invention is not to be limited to a specific antibiotic or antiseptic, because any broad-spectrum antibiotic or antiseptic can be used, as far as it is well tolerated by the patient.

The gel according to the invention is obtained by dissolving the monomeric acrylamide and methylenebisacrylamide in the required quantity of water,
20 so that a total final concentration between 0.5 and 10 per cent is achieved, adding further to the solution sodium chloride up to a concentration of 0.85 per cent, then adding more anaesthetic (0.1 to 2 per cent) and polymerization catalyst (tertiary amine, for example), accomplishing then the final purification of the ingredients stated hereto by means of an
25 adsorbent, followed by polymerization of the monomers, grinding the obtained gel twice under pressure through sieves of 0.1 up to 0.2 mm mesh resulting in particles of 0.2 up to 0.8 mm size, sterilizing and, finally, mixing the hydrogel prior to injecting with a suitable for the patient antibiotic and/or antiseptic in a concentration of 0.1 up to 0.5 per cent (w/v). The gel thus
30 obtained is drawn in through a thick cannula connected by a screw (4) to a

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syringe which is equipped with a screw-piston (1). The syringe can be made with different cubic capacity - from 0,5 up to 50 ml - depending on the quantity required for the manipulation. One end of the syringe body (3) is
5 threaded for screwing on the end-piece (2). The end-piece (2) itself is also threaded at both ends - at the one for the syringe body (3) and at the other - for the piston axle (1).

The invention relates also to a process for application of the gel. Prior to the manipulation the patient takes per os a broad-spectrum antibiotic, the
10 same antibiotic being also introduced intravenously in order to create an antibiotic barrier in the patient. The preparation proposed can be used for filling of residual body cavities resulting from operative resection of organs, for correction of congenital thoracic malformations of the "shoemaker's breasts" type, the Poland syndrome, for mammary gland neoplasia after
15 amputation due to cancer of the mammary glands and in case of aplasia or hypoplasia of the mammary glands, for correction of deformed cicatrices, as well as retracted amputation stumps according to the artificial limb prepared for the patient in the beginning.

The good tolerability of the gel makes the latter applicable to different
20 zones of the body for augmentation or correction of surgical and aesthetic malformations.

Another application sphere of the gel according to the invention is its subcutaneous application for increase of the hairs on the head and further operative transplantation of well-haired skin to the zone without hair.

25 **Advantages**

According to the invention, with the application of the gel with over 3 per cent concentration of polyacrylamide, forms preserved for a practically indefinite period of time are obtained.

The introduction of the antibiotic in the gel leads to a considerable
30 reduction of the danger of infection. During over 100 implantations made so

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far, practically no infection of the round-the-gel area and no rejection of the gel was observed in patients with an antibiotic barrier created prior to the manipulation.

- 5 The equal distribution of the antibiotic in the harder gels became possible after grinding of the said gels. The phase during which the antiseptic or the antibiotic is introduced, that is, after the thermal sterilization of the gel, allows both selection of a preparation suitable for the patient and use of thermally unstable preparations, i.e. the proposed process does not put
10 limitations to the selection of antimicrobial preparations.

The present invention enables the replacement of harder consistency tissues by the use of ground gels with higher polyacrylamide concentration. An essential improvement of the technique of drawing in and injection of the gel is the use of a syringe with a cubic capacity from 0,5 up to 50 ml,
15 equipped with a special end-piece and a screw-piston. Thus the operator is able to reduce the physical effort required for aspiration and pushing of the gel through thin needles. This is especially true for gels of higher viscosity. The improvement provides precise dosing of the quantity of gel introduced in the tissues, which after all helps for the more precise work of the
20 operator.

Explanation of the enclosed drawing

The drawing represents a syringe comprising a screw-piston (1), an end-piece (2), a main body (3) with a working volume of 0,5 up to 50 ml, and an adapter with a screw (4) for the cannula and the needle.

25 **Exemplary embodiments of the invention**

Example 1. Preparation of low concentration gel

The monomers acrylamide and methylenebisacrylamide are diluted in quantity of water required to achieve total final concentration of 3 per cent (w/v). NaCl is added to the solution so that the final concentration of same
30 becomes 0.85 per cent (w/v), then the anaesthetic Lidocaine - up to 0.2 per

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cent (w/v) and a minimum quantity of tertiary amine as polymerisation catalyst. pH of the solution is maintained between 6.5 and 8.0. It is not necessary to set precisely the acidity of the solution because of the extremely low buffer capacity of the latter. Activated carbon for final elimination of eventual pyrogenic substances and other undesired admixtures is added and the solution is stirred at ambient temperature for an hour. The solution is filtered, then persulphate as an initiator of polymerization is added. When the polymerization is completed the perfectly clear gel obtained is ground by passing the latter at least twice through a metal net with 0.1 up to 0.2 mm mesh under a pressure of 4 atmospheres until particles of 0.2 up to 0.8 mm size are obtained. A slightly opalescent mass is obtained due to the appearance of many surfaces between the liquid and the gel phase. The gel is then subjected to sterilization using standard thermal processing. One hour prior to the correction of the patient's tissues antibiotic Rocephine is injected into the gel with a syringe in small doses (0.1 ml) in different areas up to a final concentration of 0.2 per cent (w/v). The gel is then tempered at 37°C and an hour after the introduction of the antibiotic is waited to enable the equal distribution of the latter in the gel by diffusion. The mass obtained can be quite easily taken by a thick needle put in a syringe according to the drawing enclosed herein, and then injected into the patient with a thin needle for correction of his malformations.

Example 2. Preparation of a medium polyacrilamide concentration gel

Same as example 1, except that the final concentration of the gel is 4 per cent and the latter is ground under a pressure of 5-6 atmospheres. The result in this case is that the reshaped tissue preserves its form and no reduction of its volume has been observed.

Example 3. Preparation of high polyacrylamide concentration gel.

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Same as example 1, except that after polymerization of the monomers the final concentration of which is 5 per cent (w/v) in this case, the gel obtained is ground under a pressure of 6 atmospheres. The process is facilitated by the addition of a physiological solution enriched by 0.2 per cent of Lidocaine.

Example 4.

The manipulations are repeated as in example 1, 2 or 3, except that antibiotic Gentamycin in a concentration of 0.02 per cent (w/v) is used.

10 Example 5.

The manipulations are repeated as in example 1, 2 or 3, except that antibiotic Cephalexin in a concentration of 0.5 per cent (w/v) is used.

Example 6.

The manipulations are repeated as in example 1, 2 or 3, except that antibiotic Amikacin in a concentration of 0.5 per cent (w/v) is used.

Example 7.

The manipulations are repeated as in example 1, 2 or 3, except that antiseptic 5-Nitrox in a concentration of 0.01 per cent (w/v) is used.

Example 8. Application of the gel

20 Prior to the manipulation the patient takes per os a broad-spectrum antibiotic like Ciprobay (0.4 g), and 1.0 g Rocephine is introduced in the patient intravenously in order to create in him an antibiotic barrier. After surgical cleaning of the entire thorax and the two mammary glands, the operative area is surrounded by sterile linen. A local anaesthesia of the skin is made consecutively on the two breasts, in the base of the mammary glands, in three spots at a distance of 120°. The gel prepared according to example 1 or 2 is introduced with a syringe through the anaesthetised skin behind the parenchyma of the mammary glands, depending on the volume of the latter. The average quantity varies between 150 and 200 ml per

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breast. During the injection the identical volume of the two mammary glands is controlled.

Example 9. Application of the gel.

- 5 Antibiotic barrier is created and the patient is anaesthetised according to example 8. The gel prepared according to example 3 is introduced through puncture openings into the amputation stump until the clearance between the artificial limb and the retracted amputation stump is filled and the patient feels the artificial limb comfortable again.

- 10 Example 10. Application of the gel.

Gel prepared according to example 3 is introduced in special places of a two-wall artificial limb until the clearance between the artificial limb and the retracted amputation stump is filled and the patient feels the artificial limb comfortable again.

Patent Claims

1. An injectable, biocompatible, hydrophilic gel for replenishment of missing areas of man's and mammals' soft tissue or for increasing the turgor of the said soft tissue the said gel containing polyacrylamide and an anaesthetic, characterized in that the polyacrylamide concentration is between 0.5 and 10 per cent (w/v) and that the gel contains also a well-tolerated by the patient antibiotic and/or antiseptic in concentrations between 0.01 and 0.5 per cent (w/v) and the gel particles are between 0.005 and 2 mm.
2. A gel according to claim 1, characterized in that the gel particles are between 0.2 and 0.8 mm.
3. A gel according to claim 1, characterized in that the antibiotic well-tolerated by the patient can be selected from the group of antibiotics including Rocephine, Gentamycin, Cephalexin, Amikacin and others.
4. A gel according to claims 1 to 3, characterized in that the antiseptic can be selected from the group of antiseptics including 5-Nitrox, Nelidix, Flagyl, etc.
5. A process for the preparation of a gel according to claims 1 to 4 wherein the monomeric solution of the acrylamide and methylenebisacrylamide containing an anaesthetic and a catalyst is depirogenised, filtered, polymerized and sterilized, characterized in that the polymeric product in concentrations from 0.5 up to 10 per cent (w/v) is ground to particle size between 0.005 and 2 mm prior to the sterilization phase and about an hour before injection of the gel into the patient a well-tolerated by the patient antibiotic and/or antiseptic is added to the gel in concentration between 0.01 and 0.5 per cent (w/v).
6. A process for application of the gel according to claims 1 to 5, characterized in that an antibiotic barrier is created in the patient prior

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to the introduction of the gel, the said patient taking parentherally or per
os a well-tolerated by him antibiotic or antiseptic.

- 5 7. A syringe for aspiration and injection of the gel according to claims 1 through 4, characterized in that the syringe comprises a screw-piston (1), an end-piece (2), a main body (3) with a working volume of 0,5 up to 50 ml, and an adapter with a screw (4) for the cannula and the needle.

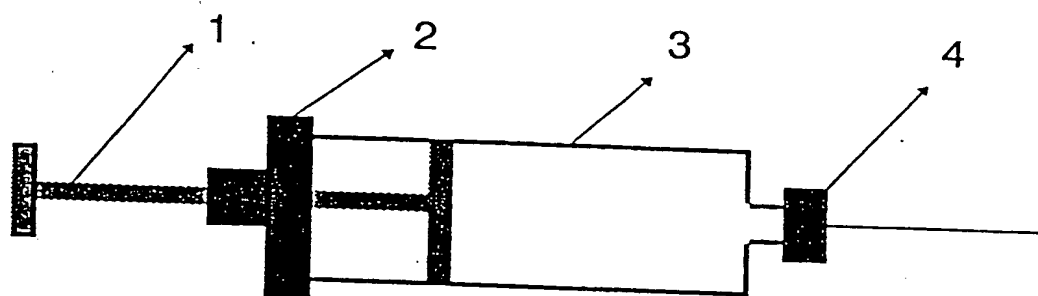


FIG.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/BG 98/00011

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 784 987 A (MENTOR CORP) 23 July 1997 see claims 18,19	1,3,4
Y	see column 4, line 57 - column 5, line 2 see column 6, line 6 - line 25 see column 7, line 38 - column 9, line 20 ---	1,2,5
Y	EP 0 499 164 A (BARD INC C R) 19 August 1992 see column 2, line 43 - column 3, line 8 see column 3, line 51 - line 58 see column 4, line 49 - line 52 see examples 12,13 see claims 1,10,11 ---	1,2,5
Y	EP 0 301 966 A (TRAGER SEYMOUR F ;CHYLINSKI VICTORIA S (GB)) 1 February 1989 see the whole document ---	1-3
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

9 February 1999

Date of mailing of the international search report

16/02/1999

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/BG 98/00011

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 742 022 A (INTERFALL MVP) 13 November 1996 see the whole document	1-3
X	DE 10 35 858 B (SKÄRHAMN F L) 7 August 1958 see figure 2	7
X	FR 1 364 845 A (ELLMAN I A) 23 October 1964 see figures 1,2	7
X	FR 1 098 727 A (ANAVE R) 18 August 1955 see figures 1-3	7

INTERNATIONAL SEARCH REPORT

International application No.

PCT/BG 98/00011

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 6
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claim 6 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Claims Nos.: 6

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/BG 98/00011

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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